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Nipple-sparing mastectomy in breast cancer patients: The role of adjuvant radiotherapy (Review)

STEFAN JANSSEN^{1,2}, EDNA HOLZ-SAPRA³, DIRK RADES², ALEXANDER MOSER⁴ and GABRIELA STUDER³

¹Medical Practice for Radiotherapy and Radiation Oncology, Hannover; ²Department of Radiation Oncology, University of Luebeck, Luebeck, Germany; ³Department of Radiation Oncology, University Hospital Zurich, Zurich, Switzerland; ⁴Department of Gynecology and Obstetrics, Nordstadt Hospital, Hannover, Germany

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Abstract. The present study aimed to evaluate the role of adjuvant radiotherapy (RT) following nipple-sparing mastectomy (NSM) for patients with ductal carcinoma *in situ* and invasive breast cancer, based on the published literature. Currently, there is no standard for RT following NSM. NSM aims to spare the nipple areola complex (NAC) without compromising locoregional control. Long-term follow-up studies have begun to show promising results. A search of the English literature was performed using the Medline database and Cochrane central library, with the keywords 'nipple/areola-sparing mastectomy', 'whole skin mastectomy' and 'NAC preservation'. A total of 32 original studies with data on NSM in terms of locoregional control, NAC control, NAC necrosis and adjuvant RT were identified. The median locoregional and NAC recurrence rates were 3.2 and 1.4% (range, 0-28.4% and 0-3.7%), respectively. The volume of remaining breast tissue following NSM was reported inconsistently. In 15 studies, RT was not mentioned. In the remaining 17 studies, RT was administered in 0-100% of patients. Only 7 studies provided detailed information regarding the use of adjuvant RT. Adjuvant thoracic wall irradiation was not used in certain studies, not even for locoregionally advanced tumors. Overall, NSM appears a feasible treatment without increased risk of locoregional recurrence for selected patients. The role of adjuvant RT following NSM requires further clarification. The decision regarding adjuvant RT must be made in interdisciplinary tumor boards and with consideration of the individual situation of the patient.

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1. Introduction

Breast-conserving therapy (BCT) is the gold standard for the majority of patients with localized breast cancers. In ~25% of breast cancer patients, a mastectomy is indicated for multi-centric or large tumors, and for local recurrence following BCT (1). Radical mastectomy is disfiguring, with removal of all the skin, the sub-mammalian fold and the nipple-areola complex (NAC). As a consequence, skin-sparing techniques have been introduced and demonstrated to provide similar outcomes compared with radical mastectomy (2). A study by Gerber *et al* (3) was the first to describe nipple-sparing mastectomy (NSM), which additionally saved the NAC, aiming to improve the esthetics and psychological results. The indications of NSM have been extended from a prophylactic scenario and small tumors distant from the NAC to larger and multi-centric tumors (4,5). There are several studies and reviews on NSM (1,2,5-10), a number of which focus on oncological safety (3,11-24), cosmetic outcome (24-29) and surgical techniques (24-32). The role of adjuvant radiotherapy (RT), including dose-fractionation concepts and techniques (6), remains unclear.

This review focuses on the use of adjuvant therapy following NSM to further clarify its role in the setting of this surgical technique.

2. Database search

A systematic review of the English literature was carried out using the Medline database and Cochrane Central Library.

Correspondence to: Dr Stefan Janssen, Medical Practice for Radiotherapy and Radiation Oncology, GSR Rundestrasse 10, Hannover D-30161, Germany
E-mail: st-janssen@gmx.net

Key words: nipple-sparing mastectomy, radiotherapy, breast cancer

Keywords were 'nipple/areola-sparing mastectomy', 'whole skin mastectomy', 'NAC preservation' and 'adjuvant radiotherapy'. Each study presenting data on nipple-sparing mastectomy in ductal carcinoma *in situ* (DCIS) or breast cancer patients was reviewed focusing on the use of adjuvant RT. In addition, data on locoregional control, NAC control and NAC necrosis were collected. Studies reporting exclusively on prophylactic NSM and studies with <10 patients were excluded. The majority of study groups reported on NSM in a prophylactic setting and NSM for invasive cancer, however, the present review was limited to data from patients with DCIS and invasive breast cancer, as RT is not used in the prophylactic setting.

3. Indications of NSM

A total of 32 original studies concerning NSM in patients with DCIS and/or invasive cancer were identified. In 11 studies, the inclusion criterion for NSM was small tumors >1-2 cm distant from the NAC (1,33). In 21 studies, locally advanced and multi-centric tumors were included (4,34,35). Only 5 studies excluded T3/4 tumors and patients with ≥ 4 positive lymph nodes. Recent data has shown an increasing use of NSM in the more advanced disease stages (4,34). It is generally agreed that involvement of the skin/NAC (1), inflammatory tumors (2) and Paget's disease (3) are contraindications for NSM. Undetected tumor involvement of the clinically non-involved NAC is a critical point. In a previous study, the rate of histopathological NAC involvement in patients treated with NSM ranged between 0 and 58% (6). Risk factors for involvement are tumor location, number of positive lymph nodes and lymphovascular invasion (36). Tumor size and distance from the NAC, as measured by magnetic resonance imaging, are correlated with an increased risk of NAC involvement (37). Almost all studies identified used intraoperative pathological assessment (frozen sections) of the subareolar tissue for deciding whether NSM could be carried out or not. In cases of involvement of the NAC, the complex was not spared (25,29,33).

4. Oncological outcome and complications

The number of patients included in the identified studies ranged from 26 to 1,001 patients (median, 147 patients), and the follow-up period ranged from 10 to 156 months (median, 38.4 months). The data for these studies is summarized in Table I. In total, 8 studies provided follow-up data for 5 years or longer. The majority of the studies focused on oncological feasibility (locoregional control), safety and cosmetic outcomes. Locoregional recurrence in the treated breast occurred in 0-28.4% of cases (median, 3.2% of cases) and recurrence in the NAC in 0-3.7% of cases (median, 1.4% of cases). The rate of total NAC necrosis and partial NAC necrosis ranged from 0-10% and 0-28.2%, with median values of 4.4 and 6.8%, respectively. Only one study addressed the potential impact of post-operative radiation on NAC necrosis: Carlson *et al* observed no difference in nipple necrosis with (n=9) or without (n=36) the application of RT (32).

5. Adjuvant RT

In 15 studies, the administration of adjuvant RT was not mentioned. A total of 10 studies reported the percentage of

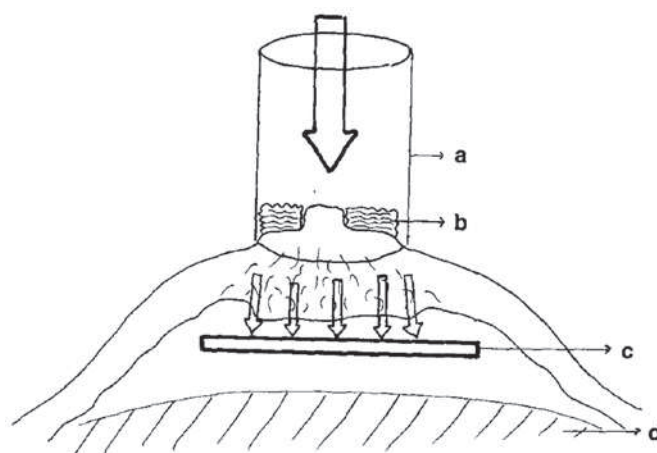


Figure 1. Electron intraoperative radiotherapy. a, sterile collimator of the linear accelerator; b, gauze over areola; c, protective lead; d, pectoralis major muscle. Figure reproduced from Petit *et al* (42) with permission.

patients treated with adjuvant RT without providing more details with respect to indication, technique and prescribed doses, while 7 studies described at least the indication for adjuvant RT. In total, RT was administered in 6 to 100% of patients according to 17 analyses.

Sakurai *et al* reported a study of 788 patients without adjuvant RT following NSM in Union for International Cancer Control stage 0-IV patients (38). The locoregional recurrence rate of 8.2% and the NAC recurrence rate of 3.7% were comparable to the rates of other studies (Table 1) (3,4,12-36,38-40,47,49).

Burdge *et al* (34) and Boneti *et al* (25) delivered 50 Gy to the thoracic wall (with or without lymphatic drainage) for tumors >5 cm and/or in cases with ≥ 4 positive lymph nodes. Moyer *et al* applied RT for resection margins ≤ 1 mm (28). In another study, the application of 50 Gy to the thoracic wall depended only on the treating physician's decision (proportion of irradiated patients not mentioned) (13).

Petit *et al* (42) performed RT exclusively to the NAC as either electron intraoperative RT (ELIOT; Fig. 1) (42) or as a single dose of 16 Gy (electron beams) a few days after surgery. The study reported a rate of locoregional recurrence of 1.4%, with all recurrences distant from the NAC. The outcomes were not significantly different between the patients receiving ELIOT (n=800) and those receiving delayed post-operative RT (n=201) (29). In six other studies providing statements on RT, a dose of 50 Gy was applied to the thoracic wall using conventional fractionation, with daily doses of 2 Gy administered on 5 days per week (13,14,18,25,28,34). In the study by Rulli *et al*, the decision for adjuvant RT was based on the remaining breast tissue, with residual glandular tissue as an indication for RT (n=10) and no remaining tissue after NSM as an indication for withholding RT (n=50) (18). Only one study group found a significant difference in locoregional recurrence rate depending on the application of RT, as determined in 216 patients (8.5% with RT vs. 28.4% without RT) (12). The tumor stage contributions in the two groups were not supplied. No observations of a higher rate of NAC necrosis following the application of adjuvant RT were reported.

No study was found commenting on the radiation boost volume, including the NAC area.

Table I. Studies with therapeutic nipple-sparing mastectomy.

First author, year	No. of patients	FU, months	Stage	RT, % (technique)	LRR recurrence, %	NAC recurrence, %	NAC necrosis, %	Breast tissue remaining ('citation' from study)
Gerber <i>et al</i> , 2003 (3)	60	101	0-IIIB	27% (technique NA)	NA	11.7	NA	NA
Komorowski <i>et al</i> , 2006 (47)	38	NA	DCIS, I-III	NA	NA	NA	7.9 (total), 5.3 (partial)	NA
Caruso <i>et al</i> , 2006 (49)	50	66	0-III	6% (technique NA)	2	2	2	'Removal of as much as possible of the entire gland'
Sacchini <i>et al</i> , 2006 (23)	64	24.6	DCIS, T1-2	NA	1.3	0	11	NA
Benediktsson and Perbeck, 2008 (17)	216	156	0-III	21.8% (technique NA)	8.5% with RT	NA	NA	'5 mm gland tissue left beneath the NAC'
Voltura <i>et al</i> , 2008 (12)	34	18	DCIS, T1-3, 29% N+	15% (technique NA)	28.4% without RT	0	NA	'No nipple coring'
Crowe <i>et al</i> , 2008 (22)	83	NA	DCIS, invasive cancer	NA	0	0	1.8 (partial)	'Tissue within the nipple is completely removed'
Paepke <i>et al</i> , 2009 (40)	96	34	DCIS, invasive cancer T1-3	NA	0	0	1	'NA-skin free of ducts and gland tissue'
Chen <i>et al</i> , 2009 (31)	40	22	NA	NA	NA	NA	8.7 (total), 15 (partial)	NA
Petit <i>et al</i> , 2009 (29)	1001	20	DCIS, invasive cancer T1-3, 0-≥4 positive ln	80%: Intraoperative RT (ELIOT) to NAC with 16 Gy 20%: Delayed one shot RT to the NAC with 16Gy	1.4	0	9.0	'Thin layer of glandular tissue left beneath areola'
Babiera and Simmons, 2010 (36)	54	15	NA	NA	NA	0	7.2	'Dissection should be at a minimum carried to the base of the NAC'
Sakamoto <i>et al</i> , 2010 (15)	87	52	0-IIIA (15% ≥4 positive ln)	30% (technique NA)	0	0	10 (total), 7.9 (partial)	'Nipple coring 19% (removal of tissue within the nipple through an additional incision)'
Kim <i>et al</i> , 2010 (21)	152	60	0-IIIA	NA	2	1.3	9.6 (total)	'1-2 mm intact dermis beneath the NAC'
Djohan <i>et al</i> , 2010 (26)	66	50.4	DCIS, invasive cancer	NA	NA	NA	2.6 (partial)	NA
Harness <i>et al</i> , 2011 (14)	40	18.5	0-IV	27.5%: Post-operative RT to the mastectomy side, axillary and supraclavicular regions 8.5%: 50 Gy for tumors >5 cm or ≥4 positive ln NA	0	0	5	'No breast tissue is left under the areola and nipple'
Boneti <i>et al</i> , 2011 (25)	281	25.3	I,II	NA	6	NA	7.1	'Complete removal of breast ductal system'
Spear <i>et al</i> , 2011 (19)	53	30	DCIS, invasive cancer	NA	NA	0	2 (total), 2 (partial)	'NAC is separated from the underlying breast'
de Alcantara Filho <i>et al</i> , 2011 (33)	157	10.38	0-IIIA	NA	0	0	3.3	'5 mm flap beneath the NAC'
Moyer <i>et al</i> , 2012 (28)	26	NA	0-III	11.5%: Adjuvant external beam RT for close margins (≤1 mm)	NA	NA	37.5 (partial)	NA
Stanec <i>et al</i> , 2014 (24)	252	63	0-IIIB	NA	3.7	1.2	10.1	'Removal of all breast tissue'
Shi <i>et al</i> , 2012 (13)	35	68	I-III	50 Gy optional depending on the treating physician	5.7	2.8	5.7	NA

Table I. Continued.

First author/s, year	No. of patients	FU, months	Stages	RT, % (technique)	LRR recurrence, %	NAC recurrence, %	NAC necrosis, %	Breast tissue remaining (citation from study)
Warren Peled <i>et al</i> , 2012 (35)	412	28	0-IV	26.7% (technique NA)	2.4	1.5	1.5 (total), 2 (partial)	'Complete excision of all nipple tissue'
Sakurai <i>et al</i> , 2013 (38)	788	78	0-IV	No RT	8.2	3.7	0	'All fat and glandular tissue removed'
Rulli <i>et al</i> , 2013 (18)	77	50	DCIS, invasive cancer T1-2, 0->3 positive ln	16.6%; 50 Gy thoracic wall for remaining tissue 83.4%; no RT for complete tissue removal	3.3	3.3	0	'Complete removal or max. 5 mm tissue remaining'
Coopey <i>et al</i> , 2013 (4)	315	22	DCIS, invasive cancer T1-T3, 13.8% positive ln	NA	2.6	0	1.7 (total)	NA
Burdge <i>et al</i> , 2013 (34)	39	18	IIB-III	100%; 50 Gy for tumors >5 cm or ≥4 positive ln (if not irradiated before)	10.3	0	NA	NA
Carlson <i>et al</i> , 2014 (32)	40	NA	DCIS, I-IV	12.7% (technique NA)	NA	NA	28.2 (partial)	'Ducts were excised from the undersurface of the nipple'
Stolier and Levine, 2013 (30)	94	NA	Invasive cancer, DCIS	NA	NA	NA	0.8 (total), 1.6 (partial)	'The NAC was elevated just beneath the level of the deep dermis'
Salibian <i>et al</i> , 2013 (27)	118	33.5	DCIS, invasive cancer T1-3	NA	5	NA	3 (total), 11 (partial)	'Removal of the entire breast tissue adherent to the areola'
Fortunato <i>et al</i> , 2013 (16)	121	26	DCIS, I-III	19%; e.g., for close margins, (technique NA)	0.8	0	4.3 (total)	'Complete removal of the glandular tissue behind the NAC'
Tancredi <i>et al</i> , 2013 (20)	58	21.7	Invasive cancer T1-3, N1-3, 5.6% >10 positive ln	NA	3.6	3.6	3.6 (partial)	'Removal of all breast parenchyma'
Munhoz <i>et al</i> , 2013 (39)	106	65.6	DCIS, invasive cancer T1-2	9.4% (technique NA)	3.7	NA	5 (partial)	NA
Total	2625	10-156 (median, 38.4)		0-100%	0-28.4 (median, 3.2)	0-3.7 (median, 1.4)		

NA, not available; DCIS, ductal carcinoma *in situ*; RT, radiotherapy; ln, lymph nodes; FU, follow-up; LRR, locoregional recurrence; NAC, nipple areola complex; ELIOT, electron intraoperative RT.

6. Cosmesis

Djohan *et al* (26) demonstrated high patient satisfaction rates with the appearance of the NAC following NSM, as determined by self-assessment and assessment by independent observers in a cohort of 141 patients, with a median follow-up period of 8 years. Other studies confirmed these good cosmetic outcomes (25,27,28). Petit *et al* (29) achieved a global result of 8/10, as rated by patients and surgeons, respectively, following ELIOT. Radiodystrophy, such as teleangiectasia, have been observed in 5.1% of 898 cases (39). None of the study groups reported an impaired cosmetic outcome following the addition of adjuvant RT.

7. Disease control

According to the reviewed literature, NSM appears a feasible option without an increased risk of locoregional recurrences for selected patients with invasive breast cancer and/or DCIS (12-16,19-24,39,40). Including a wide range of tumor (T) and node (N) stages, and tumor distances from the NAC, the overall NAC recurrence rates were low, ranging from 0-3.7% (Table I).

8. Complications

As the majority of studies removed all breast tissue under the NAC, necrosis due to compromised blood supply is a significant complication to consider. Algaithy *et al* (41) and Gould *et al* (43) found a positive correlation between a higher rate of NAC necrosis and smoking history, type of incision, body mass index and hypertension/diabetes mellitus. The wide variation in percentage of NAC necrosis (0-28.2%) could be explained by the lack of a standardized surgical technique (6).

None of the studies describing adjuvant RT revealed increased rates of partial or complete NAC necrosis following adjuvant RT. Only the study by Burdge *et al* (34), in which high-risk patients were treated with NSM and an adjuvant RT dose of 50 Gy to the thoracic wall, recorded complication rates following adjuvant RT. The study divided the complications into non-breast-related (6.7%), such as radiation pneumonitis, and breast-related (30.8%) complications. The study concluded NSM to be feasible in patients requiring adjuvant RT, with complication rates similar to those following conventional mastectomy. In order to avoid increased complication rates a delayed reconstruction was suggested following completion of RT (34).

9. NSM and adjuvant RT

Of the 32 studies with primary data on NSM in DCIS and/or invasive breast cancer included in the present review, only 7 provided detailed information on adjuvant RT, while 15 studies did not mention the use of RT following NSM. Therefore, it remains unclear if RT was administered but not mentioned or more likely, not administered at all. The majority of studies used conventionally fractionated RT to the thoracic wall (and lymphatic drainage) in high-risk groups with tumors >5 cm and/or with ≥ 4 involved lymph

nodes or close margins (25,28,34). In the study by Rulli *et al*, RT was only performed in patients with remaining breast tissue after surgery (18). The largest contribution to the role of RT following NSM has been made by Petit *et al* (42). The study initially described an intraoperative approach with a 16-Gy dose (electron beams) to the NAC with a margin of 1 cm around the areola (ELIOT; Fig. 1), which is believed to be equivalent to a 40-45-Gy fractionated dose according to the linear-quadratic model (10). In 2009, the study group reported on a large patient cohort of 1,001 patients treated with either ELIOT (n=800) or delayed RT (16-Gy single dose a few days post-surgery; n=201) (29). The treatment outcomes in terms of locoregional control were similar. To the best of our knowledge, the only study showing a significant difference in locoregional control based on the application of RT following NSM was the study by Benediktsson and Perbeck (17). This may be explained by the fact that in every patient a plate of gland tissue (thickness, 5 mm) with a 2 cm diameter was left around the NAC. According to national guidelines for BCT this would have been an indication for RT in any case (44-46). No comments were found on boost application/boost doses applied to the NAC.

In addition, there are two critical points to consider: 21 of the identified studies included high-risk patients with $\geq T3$ tumors and/or lymph node involvement of ≥ 4 positive lymph nodes, and did not comment on adjuvant RT (5,20,21,27,33,38,40,47). For advanced TN stages, several recent national guidelines have recommended external beam RT to the whole thoracic wall, with or without irradiation of the lymphatic drainage system (44-46). A recent review of the Early Breast Cancer Trialists' Collaborative Group found that after mastectomy and axillary dissection, RT reduced recurrence and breast cancer mortality in women with 1-3 positive lymph nodes, even when systemic therapy was applied (48).

Petit *et al* (29) performed intraoperative RT (IORT) using a 16-Gy single dose exclusively to the NAC, which is not in accordance with the aforementioned most recent guidelines for more advanced tumors. In the study, 21% of the patients presented with either a T3 tumor or ≥ 4 positive lymph nodes. In 2011, Petit *et al* (10) stated that conventional post-operative RT is usually delivered when patients present with high-risk factors. In the Japanese study that completely omitted RT in all patients, 12.5% of the patients presented with a stage T3 or T4 tumor (38).

The second critical point regarding the indication for RT in breast cancer patients following NSM is the amount of remaining tissue. In certain studies, a thin layer of tissue underneath the NAC was preserved, whereas in other studies, the NAC was completely removed. In the majority of patients, the entire breast tissue below the NAC was removed (Table I). Additionally, certain studies did not provide a detailed description of the surgical techniques used (3,4,9,3,26,28,47). In other studies, the aim was to remove as much breast tissue as possible (49), or to leave a certain degree of breast tissue beneath the NAC in order to ensure the blood supply of the NAC (17,18,29,33). In the latter situation, one would argue that adjuvant RT is necessary, as the remaining breast tissue is at risk for local recurrence. In cases of a T1/2N0 tumor, this could be performed with the ELIOT method, in agreement with the recommendations for

an alternative use of IORT or accelerated partial breast irradiation following breast-conserving therapy (50,51). In cases of a more advanced tumors or when IORT is unavailable, fractionated RT to the entire chest wall or post-operative single dose RT would be required. Petit *et al* (10) recommended RT to the NAC to reduce the risk of a local recurrence when breast tissue has been left behind the NAC, and if the distance between the tumor and the nipple is small. The role of a boost to the NAC is also debatable in patients with remaining breast tissue. None of the reviewed studies carried out a boost following thoracic wall RT. Omitting of RT after NSM may be discussed for low-stage tumors in patients with no remaining breast tissue behind the NAC.

10. Conclusion

Several retrospective studies have shown that NSM is a feasible option without an increased risk of local recurrences in selected patients with invasive breast cancer and/or DCIS. The surgical techniques and volume of resected breast tissue vary considerably.

Currently, there is no consensus regarding the use of adjuvant RT following NSM. For patients who meet the criteria for adjuvant RT following radical mastectomy (T3/T4, positive margins and lymph node involvement) adjuvant RT to the thoracic wall should be administered. In patients with a lower stage tumor, RT to only the NAC may be discussed. The decision for or against adjuvant RT following NSM requires an interdisciplinary tumor board, taking the benefits and potential risks for the individual patient into account.

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